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(71) Applicant: PFIZER INC.
235 East 42nd Street
New York, N.Y. 10017(US)

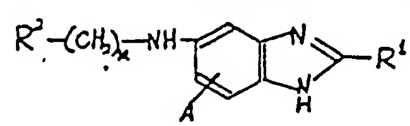
(72) Inventor: Stevens, Rodney W.
4-3-406 Seishiro-cho 2-chome
Handa-city, Aichi Prefecture(JP)
Inventor: Masami, Nakane
28-203, Kawanahonnmachi 6-chome
Show-ku, Nagoya-city, Aichi Prefecture(JP)

(74) Representative: Wood, David John et al
PFIZER LIMITED, Ramsgate Road
Sandwich, Kent CT13 9NJ(GB)

(54) **Novel benzimidazole compounds and their use.**

(57) Benzimidazole compounds and their pharmaceutically acceptable salts, as dual inhibitors of lipoxygenase and cyclooxygenase enzymes, and thus useful as antiallergy and antiinflammatory agents.

of the formula



or a pharmaceutically acceptable salt thereof:
wherein

$$R^1 \text{ is H, } -NH-R^3,\ -N(\text{loweralkyl})-R^3,\ -OR^3,\ -SR^3,\ -\text{alkylene}-R^3 \text{ or } R^4,$$

R^3 is carboxyl, loweralkyl, loweralkoxy, loweralkoyxcarbonyl, aryl or heterocyclic, which may be substituted;
R^4 is aryl or heterocyclic, which may be substituted;
R^2 is aryl or heterocyclic, which may be substituted;

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A is H or halo; and
m is an integer of 1 to 6,

NOVEL BENZIMIDAZOLE COMPOUNDS AND THEIR USE

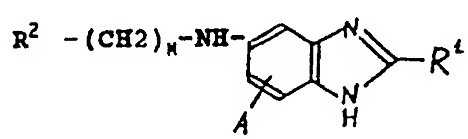
This invention relates to novel benzimidazole compounds and their use. The new compounds of the present invention are inhibitors of both the cycloooxygenase (CO) and lipoxygenase (LO) enzymes, and are of use in the treatment or alleviation of allergic or inflammatory conditions in mammals including humans.

Arachidonic acid is known to be the biological precursor of several groups of endogenous metabolites, prostaglandins including prostacyclins, thromboxanes and leukotrienes. The first step of the arachidonic acid metabolism is the release of esterified arachidonic acid and related unsaturated fatty acids from membrane phospholipids, via the action of phospholipase. Free fatty acids are then metabolized either by cyclooxygenase to produce the prostaglandins and thromboxanes or by lipoxygenase to generate hydroperoxy fatty acids which may be further converted to the leukotrienes. The prostaglandins exhibit diverse physiological effects depending upon their structure. For example, PGE and PGA inhibit gastric secretion as well as lower arterial blood pressure. The thromboxane, especially, thromboxane A2 is a potent vasoconstrictor and platelet aggregatory substance. The leukotrienes are the biological source of the slow reacting substance of anaphylaxis (SRS-A), a chemical mediator in allergic bronchial asthma.

Aspirin and most other non-steroidal antiinflammatory drugs inhibit the cyclooxygenase enzyme. Both antiinflammatory activity and analgesic activity are associated inhibition of the action of cyclooxygenase. The lipoxygenase inhibiting activity of one agent, AA861 [2,3,5-trimethyl-6-(12-hydroxy-5,10-cyclodecadiynyl)-1,4-benzoquinone], has been reported [see, Yoshimoto el al., Biochem, et Biophys. 713 , 470-473 (1982)]. CGS-5391B [(C. E. Hock et al., Prostaglandins, 28 , 557-571(1984)] has recently become known as a combined cycloxygenase and lipoxygenase inhibitor.

PCT Patent Application PCT/JP84/00452 (WO 85/01289) and Japanese patent publication No. 107958/1988 describe and claim a number of benzoxazolone and benzothiazolone derivatives useful for the treatment of inflammatory conditions and thrombosis.

The present invention is directed to compounds capable of inhibiting both cyclooxygenase and lipoxygenase. Thus, the present invention provides novel benzimidazole compounds of the formula and their use:



or a pharmaceutically acceptable salt thereof wherein R^1 is H, -NH-R^3, -N loweralkyl R^3, -OR^3, -SR^3, -alkylene-R^3 or R^4,
R^3 is carboxyl, loweralkyl, loweralkoxy, loweralkoxycarbonyl, aryl or heterocyclic, which may be substituted,
R^4 is aryl or heterocyclic, which may be substituted,
R^2 is aryl or heterocyclic, which may be substituted,
A is H or halo, and
m is an integer of 1 to 6.

In the above formula, the term "loweralkyl" means an alkyl group having 1 to 3 carbons. The term "lower alkoxy" and "lower alkoxycarbonyl" mean an alkoxy group and alkoxycarbony group, respectively, having 1 to 5 carbons, preferably up to 2 carbon atoms.

The term "alkylene" means an alkylene group having 1 to 3 carbons. The term "halo" means fluorine, chlorine, bromine or iodine. The term "aryl" means a phenyl group, naphthyl group or cyclohexyl group, and the term "heterocyclic" is one selected from the groups consisting of furyl, pyridyl, pyrimidyl, thiazolyl or thienyl, preferably pyridyl or pyrimidyl.

In the above-mentioned substituents, the aryl group and heterocyclic group may be optionally further substituted by one or more substituents. Preferable substituents are lower alkyl, lower alkoxy and halogen.

The pharmaceutically acceptable salts of the compounds of the formula (I) are those formed from acids which form non-toxic sulfate or bisulfate, phosphate, acetate, citrate, fumarate, gluconate, lactate, maleate, succinate, tartrate, methanesulfonate, benzene sulfonate and toluenesulfonate, formate salts.

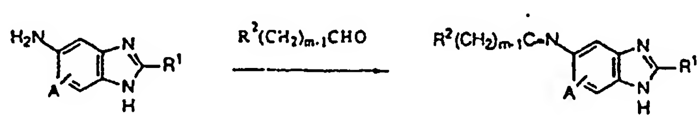
Among the especially preferred individual compounds of the present invention are:
5-(3-phenylpropyl)amino-2-(o-tolyl) benzimidazole, dihydrochloride;
2-anilino-5-benzylamino benzimidazole, dihydrochloride;

5-benzylamino-2-(3-pyridyl)amino benzimidazole, trihydrochloride;
5-benzylamino-2-propylamino benzimidazole, dihydrochloride;
5-benzylamino-2-(o-toluidino) benzimidazole, dihydrochloride;
5-benzylamino-2-(p-butylanilino) benzimidazole, dihydrochloride;
5-benzylamino-2-(α -naphthyl)amino benzimidazole, dihydrochloride;
and
2-[(N-methyl)anilino]-5-benzylamino benzimidazole.

The present invention also includes a pharmaceutical composition comprising a pharmaceutical acceptable carrier or diluent and compound of formula (I). Also embraced by the present invention is a method for treating an allergic or inflammatory condition in a mammal, especially man.

Also embraced by the present invention is a method of inhibiting the action of the lipoxygenese as well as the action of the cyclooxygenase in a mammal, which comprises administering to such mammal a lipoxygenase and cyclooxygenase inhibiting amount of a compound of formula (I).

The compounds of formula (I) may be prepared by a number of different routes. In one embodiment, they are prepared from an amino-substituted compound of the formula (II) according to the following reaction steps:



(II) (III)

$\longrightarrow$ (I)

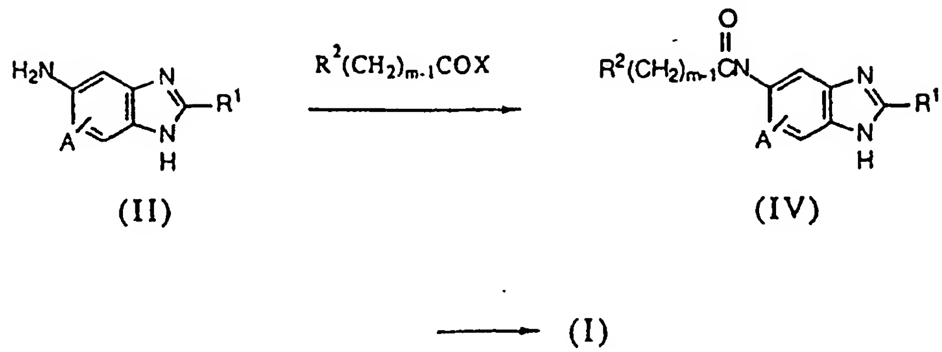
In the above formulae, R^1, R^2, m and A are as previously defined. The first step involves the treatment of compound (II) with an aldehyde, $R^2(CH^2)_{m-1}CHO$, in the presence of a dehydrating agent. The reaction is preferably conducted at ambient temperature. Higher temperatures up to 80° C can be employed without any significant disadvantage. Suitable solvents which do not react with the reactants and/or products are, for example, benzene, toluene, ethanol and tetrahyrofuran. The preferred dehydrating agent is molecular sieves, although inorganic salts such as magnesium sulfate and sodium sulfate can also be employed. When the preferred temperature is used, the reaction is substantially complete within a few hours. On completion, the product (III) can be isolated and/or purified conventionally, e,g, recrystallization or chromatography. It is, however, more convenient not to isolate this product but to subject it (i.e. in situ) to reaction conditions of the second step.

The starting materials (II) and the aldehyde $R^2(CH_2)_{m-1}CHO$ are either known compounds or may be prepared by methods reported in the art references, see e.g., D. G. Bapat and M. V. Shirsat, **Indian J. Chem.**, 3(2) ,, 81 1965, and J. Garin, E. Melendez, F. L. Merchan, C. Tejel and T. Tejero, **Synthetic Commun.**,375 **1983.**

The second step involves reduction of the C=N double bond by reaction with an appropriate hydrogen source. For example, compounds (III) may be reduced catalytically with hydrogen. It is normally achieved with a heterogeneous catalyst such as platinum (PtO_2), palladium (Pd/C) or nickel in e.g. methanol or ethanol at ambient temperature. Heating is possible but is not generally necessary.

Alternatively, the compounds may be reduced using a metal hydride. The hydride agents suitably employed in this reduction include sodium borohydride, sodium cyanoborohydride and lithium cyanoborohydride. This reaction is conducted at ambient temperature, with an excess of the hydride agent in e.g methanol or ethanol. A similar reduction using stannous chloride acid agent as a reducing agent can be carried out in methanol/aqueous hydrochloric acid. A preferred temperature for carrying out this is from 0 C to 80 C. Reduction is ordinarily complete within a few hours. The product of formula (I) is isolated by standard methods known in the art. Purification can be achieved by conventional means, such as recrystallization or chromatography.

In another embodiment, the compounds of formula (I) are prepared by the following process:



In the above formulae, R^1, R^2, m and A are as previously defined and X is an easy leaving group.

The amide (IV) is prepared by standard methods known in the art. For example, the amine (II) is reacted with an activated acid (known to those skilled in the art) such as an acid chloride, acid anhydride or activated carboxylic acid (e.g. imidazoyl derivative) in a reaction-inert solvent either in the presence or absence of a base. A wide variety of bases can be used in the reaction and they include organic amines, alkali metal hydroxides, alkaline metal corbonates, alkaline metal hydrocarbonates, alkaline earth metal hydrides and alkaline earth metal alkoxides. Preferred basic agents are triethylamine, pyridine, sodium hydroxide, potassium tert-butoxide, sodium hydride, potassium carbonate and sodium carbonate. Suitable reaction-inert solvents include methylene chloride, tetrahydofuran, benzene, tuluene, xylene and water. The reaction is usually carried out in the temperature range of 0 C to the boiling point of the solvent. Reaction times of from 30 minutes to a few hours are common. The product can be isolated and purified by conventional procedures, such as recrystallization or chromatography.

The second step usually involves reduction of the amide bond with an appropriate metal hydride. The hydride agents suitably employed in this reduction include lithium aluminum hydride, magnesium aluminum hydride, lithium trimethoxyaluminohydride, sodium bis(2-methoxyethoxy) aluminum hydride, alane and borane preferably in tetrahydrofuran, although ether or dimethoxyethane may be employed. Reaction temperature is usually 0 C through to reflux. The product of formula (I) is isolated by standard methods and purification can be achieved by conventional means, such as recrystallization or chromatography.

The pharmaceutically acceptable salts of the novel compounds of formula (I) are readily prepared by contacting said compound wth a stoichiometric amount of an appropriate mineral or organic acid in either an aqueous solution or a suitable organic solvent. The salt may then be obtained by precipitation or by evaporation of the solvent. Among those salts enumerated earlier, an especially preferred salt is the hydrochloride.

The compounds of formula (I) possess inhibiting activity on the action of the cyclooxygenase as well as on the action of the lipoxygenase. This activity has been demonstrated by a cell culture assay using rat peritoneal cavity resident cells which determines the effect of said compounds on the metabolism of arachidonic acid.

The ability of the compounds of formula (I) to inhibit both enzymes make them useful for controlling the symptoms induced by the endogenous metabolites arising from arachidonic acid in a mammalian subject. The compounds are therefore valuable in the prevention and treatment of such disease states in which the accumulation of said arachidonic acid metabolite is the causative factor, e.g., allergic bronchial asthma, skin disorders, rheumatoid arthritis, osteoarthritis, and thrombosis.

Since conventional non-steroidal inflammatory agents such as aspirin only inhibit cyclooxygenase, they suppress inflammatory conditions as well as tend to cause adverse inhibition. Compounds of the present invention, however, are gastrointestinally cytoprotective in addition to possessing anti-allergy and anti-inflammatory activities. Thus, they show less adverse effects and are of value for use as a safe drug.

When a compound of the formula (I) or a pharmaceutically acceptable salt thereof is to be used as either an anti-allergic agent or an anti-inflammatory agent, it can be administered to a human subject either alone, or preferably, in combination with pharmaceutically acceptable carriers or diluents in a pharmaceutical composition, in accordance with stand pharmaceutical practice. A compound can be administered by a variety of conventional routes of administration including oral, parental and by inhalation. When the compounds are administered orally, the dose range will be from 0.1 to 20 mg/kg body weight of the subject to be treated per day in single or divided doses. If parental administration is desired, then an effective dose will be from 0.1 to 1.0 mg/kg body weight of the subject to be treated per day. In some instance it may be

necessary to use dosages outside these limits, since the dosage will necessarily vary according to the age, weight and response of the individual patient as well as the severity of the patient's symptoms and the potency of the particular compound being administered.

For oral administration, the compounds of formula (I) can be administered, for example, in the form of tablets, powders, lozenges, syrups or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. In the case of capsules, useful diluents are lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the Ph of the solutions should be suitably adjusted and buffered.

EXAMPLES

The present invention is illustrated by the following examples. However, it should be understood that the examples are simply illustrative and the invention is not limited to the specific details of these examples. Proton nuclear magnetic resonance spectra (NMR) were measured at 60MHz unless otherwise indicated for solutions in perdeuterodimethyl sulfoxide (DMSO-d_6) and peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane. The peak shapes are denoted as follows: s, singlet,d, doublet; t, triplet; q, quartet; m, multiplet; b, broad.

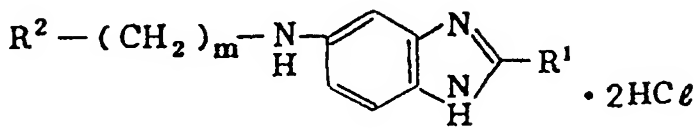
Example 1

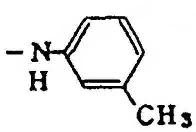
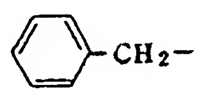
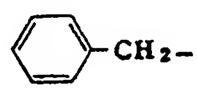
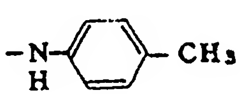
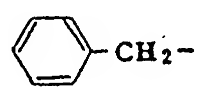
2-Anilino-5-benzylamino benzimidazole dihydrocholoride

5-Amino--2-anilino benzimidazole (4.5 m mol) and benzaldehyde (4.5 m mol) in 15 ml methanol were stirred together for one hour at room temperature. To the reaction mixture was added excess $NaBH_4$ and the reaction mixture stirred a further 30 minutes. The mixture was then concentrated under reduced pressure and resultant residue covered with saturated $NaHCO_3$, extracted into CH_2Cl_2 and dried over Na_2SO_4. Pure product was isolated by silica gel column chromatography ($CHCl_3$: CH_3OH = 15 : 1) and the resultant oil covered with HCl-CH_3OH and shaken. The resulting dihydrochloride salt was isolated by filtration to afford 2-anilino-5-benzylamino benzimidazole dihydrochloride in 73% yield.
m.p. : >275° C (dec.)
IR (KBr): 3000(br), 1680 cm^{-1}
NMR(DMSO-d_6)S: 11.79 (s, 1H), 7.56-7.20 (m, 13H) 4.47 (s, 2H)

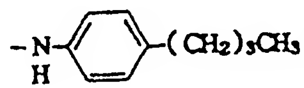
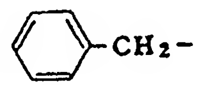
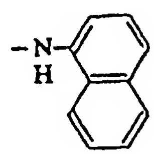
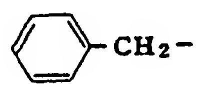
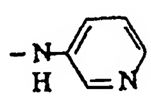
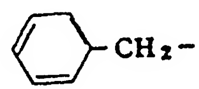
EXAMPLES

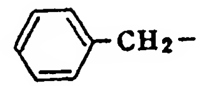
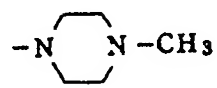
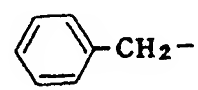
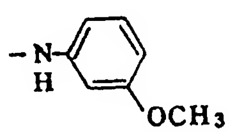
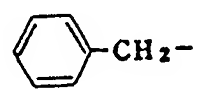
Similarly the following compounds were prepared.

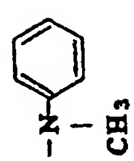
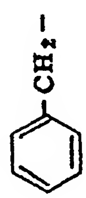
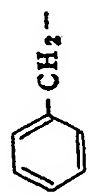
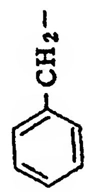


Example No	R^1	R^2-$(CH_2)_m$-		IR(KBr)	NMR
2.			268-270°C decomposed	2900(br.). 1660cm⁻¹	11.69(s.1H). 7.5-7.1(m.13H) 4.67(s,2H), 2.36(s, 3H)
3.			232-233.5°C decomposed	2900(br.). 1670cm⁻¹	7.49-7.24(m.11H). 7.11(br..1H). 4.44(s.2H). 2.29(s.3H)
4.			>270°C decomposed	3000(br.). 1700cm⁻¹	7.45-7.25(m.12H). 6.95(br.,2H). 4.40(s.2H). 2.35(s.3H)

(24)

5.			>260℃ decomposed	2900(br.). 1670cm⁻¹	11.35(s,1H) 7.45-7.43(m,3H) 7.36-7.27(m,8H) 7.0(br.2H) 4.40(s,2H) 2.61(t,J=7.3Hz,2H) 1.60-1.55(m,2H) 1.37-1.29(m,2H) 0.91(t,J=7.3Hz,3H)
6.			>235℃ decomposed	2800(br.). 1660cm⁻¹	11.71(s,1H) 8.12-8.02(m,3H) 7.74-7.59(m,4H) 7.47-7.07(m,8H) 4.43(s,2H)
7.	 ($3HC\ell \cdot 0.5H_2O$)		>270℃ decomposed	3400. 2700(br.) 1660cm⁻¹	9.29(s,1H) 8.64-8.56(m,2H) 8.00-7.94(m,1H) 7.56-7.28(m,7H) 7.16(d,J=8.1Hz,1H) 4.49(s,2H)

8.	$-\underset{H}{N}-CH_2CH_2CH_3$		205-207℃	3200, 2850, 2700	12.95(br.s,2H) 9.23(s,1H) 7.48(d,J= 5.9 Hz,2H) 7.35-7.32(m,5H) 7.10(d,J=8.8Hz,1H) 4.46(s,2H) 3.39-3.31(m,2H) 1.65-1.57(m,2H) 0.94(t,J=7.3Hz,3H)
9.	 (3HCℓ.0.5H₂O)		>280℃	3450, 2600(br.) 1650cm⁻¹	11.74(br.s,1H) 7.5-7.15(m,10H) 4.46(s,2H) 4.46-4.41(m,2H) 3.86-3.72(m,2H) 3.65-3.50(m,2H) 3.36-3.20(m,2H) 2.78(s,3H)
10.			234-237℃ decomposition	2900, 1660cm⁻¹	11.38(s,1H) 7.45-7.28(m,7H) 7.02-6.85(m,5H) 4.40(s,2H) 3.80(s,3H)

11.	 (free amine)		73.5-74.6°C		7.28-7.01(m,12H) 6.48(br.s,1H) 6.34(dd,J=8.8 および 2.2Hz,1H) 4.18(s,2H) (3.38 s,3H)
12.	$-CH_2CH_2COOCH_3$		220.9-224.2°C	3500, 2800(br.) 1740cm^{-1}	7.58-7.20(m,6H) 7.10-6.78(m,2H) 4.38(s,2H) 3.60(s,3H) 3.42-3.22(m,2H) 3.10-3.00(m,2H)
13. ($\frac{1}{2}H_2O$)	$-CH_2CH_2COOH$		200.9-202.0°C	3200, 2600(br.) 1650cm^{-1}	7.39-7.14(m,6H) 6.53(d,J=10.3Hz,1H) 6.45(s,1H) 5.95(br.s,1H) 4.27(s,2H) 2.90(t,J=7.3Hz,2H) 2.69 (t,J =7.3 Hz,2H)

Example 14

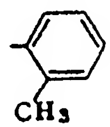
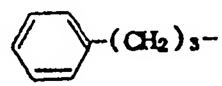
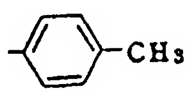
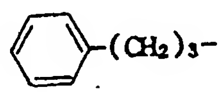
5-(3-phenylpropyl) amino-2-phenyl benzimidazole hydrochloride 5-Amino-2-phenyl benzimidazole (19 m mol) and dhydrocinnamoyl chloride (3.12 ml) in 160 ml of benzene were heated at reflux for 3 hours. After cooling the reaction mixture, the resulting precipitate was collected by filtration to afford the hydrochloride

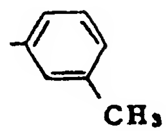
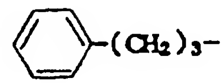
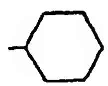
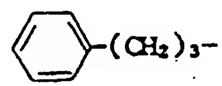
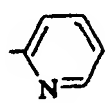
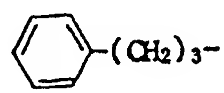
salt of the amide in 76% yield.
m.p. : 216.5 -- 219.5 °C
IR(KBr): 3350, 2800, 1660 cm^{-1}
NMR(DMSO-d_6)S: 10.45 (s, 1H), 8.41 (s, 1H) 8.35-8.25 (m, 2H), 7.8-7.58 (m, 5H), 7.3-7.19 (m, 5H), 2.96 (6, J=7Hz, 2H) 2.71 (6, J=7Hz, 2H)

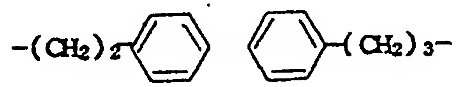
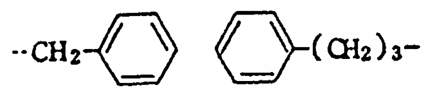
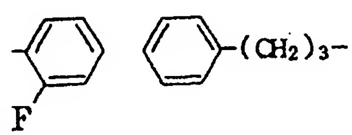
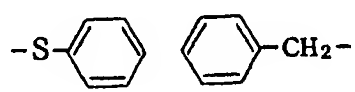
To the amide (7m mol) suspended in 50 ml THF was added $LiAlH_4$ (13 m mol) portionwise in solid form. After addition of all the $LiAlH_4$, the reaction mixture was heated at reflux for 5 hours, cooled and worked-up by standard procedure. Free alkyl amine was isolated via column chromatography (silica gel, 25% ethyl acetate in hexane) and shaken with HCl-methanol. The dihydrochloride salt was isolated by filtration to afford product in 59% yield.
m.p. : 243.9 - 245.9 °C
IR(KBr): 3450, 2700 (br.) cm^{-1}
NMR(DMSO-d_6)s: 8.37 (br., 2H), 7.73-7.70(m, 4H) 7.33-7.19(m, 7H), 3.22 (br.,2H) 2.76-2.70(m,2H), 2.05-1.92 (m,2H)

EXAMPLES 15 - 23

Similarly the following compounds were prepared.

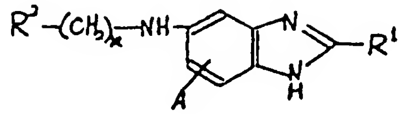
Example No.	R^1	R^2-$(CH_2)_m$-		IR(KBr)	NMR
15.			233-236℃	3450, 2700cm^{-1}	7.79-7.49(m, 5H) 7.30-7.19(m, 7H) 3.16(t, J=7.3Hz, 2H) 2.73(t, J=7.3Hz, 2H) 2.56(s, 3H) 2.03-1.90(m, 2H)
16.			245.8-248.1℃	2500cm^{-1}	8.25(d, J=8.8Hz, 2H) 7.70(d, J=8.8Hz, 1H) 7.51(d, J=8.1Hz, 2H) 7.32-7.19(m, 7H) 3.20(t, J=8.06Hz, 2H) 2.73(t, J=8.06Hz, 2H) 2.44(s, 3H) 2.01-1.90(m, 2H)

17.			>211℃ decomposed	3400. 2750(br.)cm^{-1}	8.23(s.1H) 8.19(d.J=8.8Hz.1H) 7.72(d.J=8.8Hz.1H) 7.64-7.50(m.2H) 7.40-7.12(m.7H) 3.21(t.J=8.1Hz.2H) 2.73(t.J=8.1Hz.2H) 2.45(s.3H) 1.99(m.2H)
18.			241.5-242.7 ℃	3450. 2800(br.)cm^{-1}	7.75(d.J=8.8Hz.1H) 7.58(br.s.1H) 7.42(d.J=8.8Hz.1H) 7.32-7.15(m.5H) 3.25-3.15(m.3H) 2.71(t.J=6.8Hz.2H) 2.15-1.66(m.8H) 1.45-1.20(m.4H)
19.			213.1-214.4 ℃	3400. 2650(br.)cm^{-1}	8.88(d.J=4.4Hz.1H) 8.66(d.J=8.1Hz.1H) 8.2-8.15(m.1H) 7.76-7.70(m.2H) 7.45-7.15(m.7H) 3.21(t.J=6.1Hz.2H) 2.73(t.J=6.1Hz.2H) 2.15-1.95(m.2H)

20.		270.8-272.8 ℃	2750 cm^{-1}	7.7-7.16 (m, 13H) 3.44-3.40 (m, 2H) 3.25-3.15 (m, 4H) 2.70 (t, J=7.5Hz, 2H) 2.0-1.9 (m, 2H)
21.		243.6-245℃	3450, 2800(br.) cm^{-1}	7.64 (d, J=8.1Hz, 1H) 7.49-7.15 (m, 12H) 4.5 (s, 2H) 3.20-3.10 (m, 2H) 2.70 (t, J=8.0Hz, 2H) 2.0-1.9 (m, 2H)
22.		240.6-243.3 ℃	2600(br.) cm^{-1}	8.35 (t, J=6.0Hz, 1H) 7.78 (d, J=8.8Hz, 2H) 7.63-7.45 (m, 3H) 7.50-7.15 (m, 6H) 3.22 (t, J=6.6Hz, 2H) 2.73 (t, J=6.6Hz, 2H) 2.18-1.92 (m, 2H)
23.		200-203℃	2800(br.) cm^{-1}	10.3 (br., 3H) 7.69-7.12 (m, 14H) 4.43 (s, 2H)

Claims

1) A compound of the formula



or a pharmaceutically acceptable salt thereof:
wherein R^1 is H, -NH-R^3, -N loweralkyl -R^3, -OR^3, -SR^3, -alkylene-R^3 or R^4,
R^3 is carboxyl, loweralkyl, loweralkoxy, loweralkoyxcarbonyl, aryl or heterocyclic, which may be substituted;
R^4 is aryl or heterocyclic, which may be substituted;
R^2 is aryl or heterocyclic, which may be substituted;
A is H or halo; and
m is an integer of 1 to 6.

2) A compound according to claim 1 wherein
R^1 is -NH-R^3, -N loweralkyl R^3 or R^4,
R^3 is loweralkyl, aryl or heterocyclic, which may be substituted,
R^4 is aryl or heterocyclic, which may be substituted,
R^2 is aryl,
m is 1 - 3, and
A is H or halo.

3) A compound according to claim 1 wherein R^1 is -NH-R^3,
R^3 is loweralkyl, phenyl which may be substituted, pyridyl or naphthyl,
R^4 is phenyl which may be substituted or cyclohexyl,
R^2 is phenyl,
m is 1 - 3, and
A is H or halo.

4) A compound according to claim 1
wherein R^1 is -N loweralkyl -R^3
R^3 is loweralkyl, phenyl which may be substituted, pyridyl or naphthyl,
R^4 is phenyl which may be substituted
R^2 is phenyl,
m is 1 - 3, and
A is H or halo.

5) A compound according to claim 2, 3 or 4 wherein
R^3 and R^4 are phenyl or substituted phenyl and
R^2 is phenyl and m is 1

6) A compound according to claim 1 said compound being
5-(3-phenylpropyl) amino-2- (o-tolyl) benzimidazole, dihydrochloride,
2-anilino-5-benzylamino benzimidazole, dihydrochloride;
5-benzylamino-2-(3-pyridyl)amino benzimidazole, trihydrochloride;
5-benzylamino-2-propylamino benzimidazole, dihydrochloride;
5-benzylamino-2-(o-toluidino) benzimidazole, dihydrochloride;
5-benzylamino-2-(p-butylanilino) benzimidazole, dihydrochloride;
5-benzylamino-2-(α-naphthyl) amino benzimidazole, dhydrochloride, or
2[(N-methyl) anilino]-5-benzylamino benzimidazole.

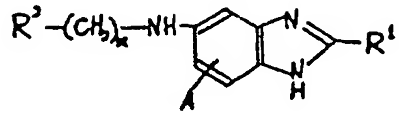
7) A pharmaceutical composition for the treatment of allergic or inflammatory conditions, which comprises a compound of claim 1 together with a pharmaceutically acceptable carrier.

8) A compound according to any one of claims 1 to 6, for use in medicine.

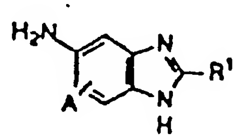
9) Use of a compound according to any one of claims 1 to 6 for making a medicament for inhibiting lipoxygenase or cyclooxygenase.

CLAIMS FOR THE FOLLOWING CONTRACTING STATES: GR, ES

1) A process for preparing a compound of the formula I



or a pharmaceutically acceptable salt thereof
wherein R^1 is H, -NH-R^3, -N loweralkyl -R^3, -OR^3, -SR^3, -alkylene-R^3 or R^4,
R^3 is carboxyl, loweralkyl, loweralkoxy, loweralkoyxcarbonyl, aryl or heterocyclic, which may be substituted;
R^4 is aryl or heterocyclic, which may be substituted;
R^2 is aryl or heterocyclic, which may be substituted;
A is H or halo; and
m is an integer of 1 to 6
characterized by reacting a compound of formula II



with an aldehyde of formula R^2 $(CH_2)_{m-1}CHO$
wherein A,R_1,R_2 and m are as previously defined followed by reduction of the resultant intermediate to give a compound of the formula I said processes being followed by optional conversion of the product into a pharmaceutically acceptable salt.

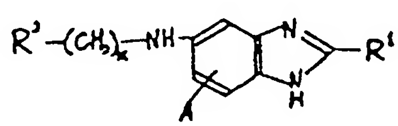
2) The process of claim 1 wherein the reaction of the formula II compound and the aldehyde occurs in the presence of a dehydrating agent and the resultant intermediate is either reduced catalytically with hydrogen or reduced with a metal hydride.

3) The process of claim 2 wherein the reaction of the formula II compound and the aldehyde occurs at a temperature up to 80 °C and the intermediate is reduced catalytically with hydrogen.

4) The process of claim 1 in which
R^1 is -NH-R^3, or -N loweralkyl -R^3 or R^4,
R^3 is loweralkyl, aryl or heterocyclic, which may be substituted,
R^4 is aryl which may be substituted and
R^2 is aryl.

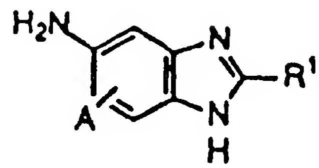
5) The process of claim 1 in which
5-(3-phenylpropyl) amino-2-(o-tolyl) benzimidazole dihydrochloride;
2-anilino-5-benzylamino benzimidazole, dihydrochloride;
5-benzylamino-2-(3-pyridyl) amino benzimidazole, trihydrochloride;
5-benzylamino-2-propylamino benzimidazole dihydrochloride;
5-benzylamino-2-(o-toluidino) benzimidazole, dihydrochloride,
5-benzylamino-2-(p-butylanilino) benzimidazole, dihydrochloride,
5-benzylamino-2-(α-naphthyl)amino benzimidazole, dihydrochloride, or
2-[(N-methyl) anilino] -5-benzylamino benzimidazole is produced.

6) A process for preparing a compound of formula I

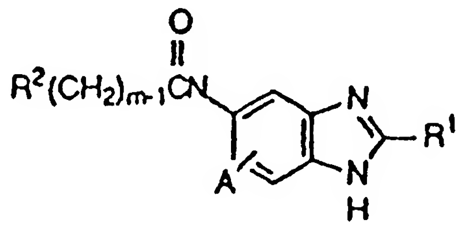


or a pharmaceutically acceptable salt thereof:
wherein R^1 is H, -NH-R^3, -N loweralkyl -R^3, -OR^3, -SR^3, -alkylene-R^3 or R^4,
R^3 is carboxyl, loweralkyl, loweralkoxy, loweralkoyxcarbonyl, aryl or heterocyclic, which may be substituted;
R^4 is aryl or heterocyclic, which may be substituted;
R^2 is aryl or heterocyclic, which may be substituted;
A is H or halo; and
m is an integer of 1 to 6

characterized by: reacting an amide formula II compound



with an activated acid to form an intermediate formula IV compound;



wherein A, R_1,R_2, and m are as previously defined; and reducing the intermediate to give a compound of formula I; said processes being followed by optional conversion of the product into a pharmaceutically acceptable salt.

7) The process of claim 6 wherein the reaction of the amide with the activated acid occurs in the presence of a base and the intermediate compound is reduced with a metal hydride.

8) The process of claim 7 wherein the reaction of the amide with the activated acid is carried out at a temperature of 0° C to reflux and the reduction is carried out at a temperature of 0° C to reflux.

9) The process of claim 1 in which
R^1 is -NH-R^3, -N loweralkyl R^3 or R^4,
R^3 is loweralkyl, aryl or heterocyclic,which may be substituted,
R^4 is aryl which may be substituted,
R^2 is aryl,
m is 1 - 3, and
A is H or halo.

10) The process of claim 6 in which 5-(3-phenylpropyl)amino-2-(o-tolyl) benzimidazole, dihydrochloride,
2-anilino-5-benzylamino benzimidazole, dihydrochloride,
5-benzylamino-2-(3-pyridyl) amino benzimidazole, trihydrochloride,
5-benzylamino-2-propylamino benzimidazole, dihydrochloride,
5-benzylamino-2-(p-butylanilino) benzimidazole, dihydrochloride,
5-benzylamino-2-(o-butylanilino) benzimidazole, dihydrochloride,
5-benzylamino-2-(α-naphthyl) amino benzimidazole, dihydrochloride, or
2[(N-menthyl) anilino]-5-benzylamino benzimidazole is produced.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 31 0199

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	CHEMICAL ABSTRACTS, vol. 69, no. 17, 21st October 1968, page 6075, column 2, abstract no. 65106g, Columbus, Ohio, US; K.H. KOEHLER et al.: "Specificity of the Amaranthus cytokinin test. III. Benzimidazoles and other compounds", & FLORA (JENA), ABT. A 1968, 159, 293-8 * Abstract *	1	C 07 D 235/30 A 61 K 31/415 C 07 D 235/18 C 07 D 235/08 C 07 D 235/28 C 07 D 401/12 C 07 D 401/04 A 61 K 31/44
X	CHEMICAL ABSTRACTS, vol. 108, no. 1, 4th January 1988, page 5911, abstract no. 5914j, Columbus, Ohio, US; V.A. KUZNETSOV et al.: "Derivatives of 5(6)-aminobenzimidazole", & ZH. ORG. KHIM. 1987, 23(3), 637-42 * Abstract *	1-2	
A	CHEMICAL ABSTRACTS, vol. 110, no. 21, 22nd May 1989, page 739, abstract no. 192707v, Columbus, Ohio, US; I.V. SKLYAROVA et al.: "Synthesis and biological activity of 5(6)-amido-and 5(6)-amino-2-arylbenzoimidazole derivatives", & KHIM.-FARM. ZH. 1988, 22(6), 697-9 * Abstract *		TECHNICAL FIELDS SEARCHED (Int. Cl.5)
A	CHEMICAL ABSTRACTS, vol. 107, n. 20, 16th November 1987, page 755, abstract no. 187218v, Columbus, Ohio, US; & JP-A-62 55 644 (KONISHIROKU PHOTO INDUSTRY CO., LTD) 11-03-1987 * Abstract *		C 07 D 235/00 A 61 K 31/00 C 07 D 401/00
A	CHEMICAL ABSTRACTS, vol. 107, no. 14, 5th October 1987, page 582, abstract no. 124494m, Columbus, Ohio, US; & JP-A-62 50 751 (KONISHIROKU PHOTO INDUSTRY CO., LTD) 05-03-1987 * Abstract *		

-/-

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	30 November 90	DE BUYSER I.A.F.

CATEGORY OF CITED DOCUMENTS

- X: particularly relevant if taken alone
- Y: particularly relevant if combined with another document of the same catagory
- A: technological background
- O: non-written disclosure
- P: intermediate document
- T: theory or principle underlying the invention
- E: earlier patent document, but published on, or after the filing date
- D: document cited in the application
- L: document cited for other reasons
- &: member of the same patent family, corresponding document

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 31 0199

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	CHEMICAL ABSTRACTS, vol. 107, no. 14, 5th October 1987, page 580, abstract no. 124477h, Columbus, Ohio, US; & JP-A-62 24 244 (KONSHIROKU PHOTO INDUSTRY CO., LTD) 02-02-1987 * Abstract *		
A	CHEMICAL ABSTRACTS, vol. 84, no. 11, 15th March 1976, page 29, abstract no. 69388j, Columbus, Ohio, US; W.C. CAMPBELL et al.: "Effect of parenterally injected benzimidazole compounds on Echinococcus multilocularis and Taenia crassiceps metacestodes in laboratory animals", & J. PARASITOL. 1975, 61(5), 844-52 * Abstract *		
A	CHEMICAL ABSTRACTS, vol. 72, no. 17, 27th April 1970, page 399, column 1, abstract no. 90461q, Columbus, Ohio, US; & ZA-A-68 00 351 (MERCK AND CO., INC.) 17-07-1969		
A	US-A-4 243 806 (A.H.M. RAEYMAEKERS et al.)		
A	EP-A-0 209 707 (Dr. KARL THOMAE)		
A	EP-A-0 312 004 (HOECHST AG)		
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	30 November 90	DE BUYSER I.A.F.

CATEGORY OF CITED DOCUMENTS

X: particularly relevant if taken alone
Y: particularly relevant if combined with another document of the same catagory
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention

E: earlier patent document, but published on, or after the filing date
D: document cited in the application
L: document cited for other reasons

&: member of the same patent family, corresponding document